NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 452

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

2,2-BIS(BROMOMETHYL)-1,3-PROPANEDIOL
(FR-1138®)

(CAS NO. 3296-90-0)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge while supplies last from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). Listings of all published NTP reports and ongoing studies are also available from NTP Central Data Management. The Abstracts and other study information for 2-year studies are also available on the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov.

NTP TECHNICAL REPORT

ON THE

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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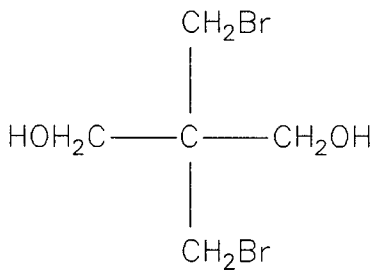
ABSTRACT



2,2-BIS(BROMOMETHYL)-1,3-PROPANEDIOL
(FR-1138®)

(Technical Grade: 78.6% 2,2-bis(bromomethyl)-1,3-propanediol, 6.6% 2,2-bis(hydroxymethyl)-1-bromo-3-hydroxypropane, 6.9% 2,2-bis(bromomethyl)-1-bromo-3-hydroxypropane, 0.2% pentaerythritol, and 7.7% dimers and structural isomers)

CAS No. 3296-90-0

Chemical Formula: $C_5H_{10}Br_2O_2$ Molecular Weight: 261.94

Synonyms: 2,2-Bis(2-bromomethyl)-1,3-propanediol; 1,3-dibromo-2,2-dihydroxymethylpropane; 1,3-dibromo-2,2-dimethylolpropane; 2,2-dibromomethyl-1,3-propanediol; dibromopentaerythritol; dibromoneopentyl glycol; pentaerythritol dibromide; pentaerythritol dibromohydrin

2,2-Bis(bromomethyl)-1,3-propanediol is used as a fire retardant in unsaturated polyester resins, in molded products, and in rigid polyurethane foam. 2,2-Bis(bromomethyl)-1,3-propanediol was chosen for study because it is a widely used flame retardant and little toxicity and carcinogenicity data were available.

Groups of male and female F344/N rats and B6C3F$_1$ mice were exposed to technical grade 2,2-bis(bromomethyl)-1,3-propanediol (78.6% pure) in feed for 13 weeks or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, cultured Chinese hamster ovary cells, mouse bone marrow, and mouse peripheral blood.

13-WEEK STUDY IN RATS

Groups of 10 male and 10 female rats were fed diets containing 0, 1,250, 2,500, 5,000, 10,000, or 20,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol for 13 weeks. These levels corresponded to approximately 100, 200, 400, 800, or 1,700 mg 2,2-bis(bromomethyl)-1,3-propanediol/kg body weight (males) and 100, 200, 400, 800, or 1,600 mg/kg (females). No rats died during the studies. The final mean body weights and weight gains of 5,000, 10,000, and 20,000 ppm males and females were significantly lower than those of the controls. Feed consumption by exposed animals was lower than that by controls at week 1, but was generally similar to or slightly higher than that by controls at week 13. No chemical-related clinical findings were observed. Chemical-related differences in clinical pathology parameters included increased urine volumes accompanied by decreased urine specific gravity and minimally increased protein excretion in 10,000 and 20,000 ppm males. In females, urine parameters were less affected than males. Water deprivation tests demonstrated that male and female rats were able to adequately concentrate their urine in response

to decreased water intake. Serum protein and albumin concentrations in female rats exposed to 2,500 ppm and higher were slightly lower than those of the controls. Renal papillary degeneration was present in 5,000 and 10,000 ppm males, and in 20,000 ppm males and females. Hyperplasia of the urinary bladder was present in 20,000 ppm males.

13-Week Study in Mice

Groups of 10 male and 10 female mice were fed diets containing 0, 625, 1,250, 2,500, 5,000, or 10,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol for 13 weeks. These levels corresponded to approximately 100, 200, 500, 1,300, or 3,000 mg 2,2-bis(bromomethyl)-1,3-propanediol/kg body weight (males) and 140, 300, 600, 1,200, or 2,900 mg/kg (females). One control female, two males and one female receiving 625 ppm, one female receiving 1,250 ppm, one female receiving 2,500 ppm, one female receiving 5,000 ppm, and three males receiving 10,000 ppm died during the study. The final mean body weights and body weight gains of males and females receiving 1,250, 2,500, 5,000, or 10,000 ppm and of females receiving 625 ppm were significantly lower than those of the controls. Feed consumption by exposed mice was generally higher than that by controls throughout the study. Clinical findings included abnormal posture and hypoactivity in 10,000 ppm male and female mice. Blood urea nitrogen concentrations of 5,000 ppm females and 10,000 ppm males and females were greater than those of controls. Also, urine specific gravity was lower in 10,000 ppm females. Differences in organ weights generally followed those in body weights. Papillary necrosis, renal tubule regeneration, and fibrosis were observed in the kidneys of 2,500 and 5,000 ppm males and 10,000 ppm males and females. Urinary bladder hyperplasia was observed in 5,000 and 10,000 ppm males and females.

2-Year Study in Rats

Groups of 60 male and 60 female rats received 2,500, 5,000, or 10,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed for 104 to 105 weeks. Groups of 70 males and 60 females received 0 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed for 104 to 105 weeks. A stop-exposure group of 70 male rats received 20,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed for 3 months, after which animals received undosed feed for the remainder of the 2-year study. Average daily doses of 2,2-bis(bromomethyl)-1,3-propanediol were 100, 200, or 430 mg/kg body weight for males and 115, 230, or 460 mg/kg for females. Stop-exposure males received an average daily dose of 800 mg/kg. Ten animals from the 0 ppm male group and the 20,000 ppm stop-exposure group were evaluated at 3 months; nine or 10 control animals and five to nine animals from each of the continuous-exposure groups were evaluated at 15 months.

Survival, Body Weights, Feed Consumption, and Clinical Findings

Survival of 5,000 and 10,000 ppm continuous-exposure study males and females and 20,000 ppm stop-exposure males was significantly lower than that of the controls. Mean body weights of exposed male and female rats receiving 10,000 ppm and stop-exposure males receiving 20,000 ppm were lower than those of the controls throughout most of the study. In the continuous-exposure study, feed consumption by exposed rats was generally similar to that by controls throughout the study. In 20,000 ppm stop-exposure males, the feed consumption was lower than that by controls. Clinical findings included skin and/or subcutaneous masses on the face, tail, and the ventral and dorsal surfaces of exposed rats.

Pathology Findings

In the 2-year continuous and stop-exposure studies in male rats, exposure to 2,2-bis(bromomethyl)-1,3-propanediol was associated with neoplastic effects in the skin, mammary gland, Zymbal's gland, oral cavity, esophagus, forestomach, small and large intestines, mesothelium, urinary bladder, lung, thyroid gland, hematopoietic system, and seminal vesicle. Nonneoplastic effects in the kidney, lung, thyroid gland, seminal vesicle, pancreas, urinary bladder, and forestomach were also observed. In females, 2-year exposure to 2,2-bis(bromomethyl)-1,3-propanediol was associated with neoplastic effects in the oral cavity, esophagus, mammary gland, and thyroid gland. Nonneoplastic effects in the kidney were also observed. These findings are outlined in the two summary tables.

2-YEAR STUDY IN MICE

Groups of 60 male and 60 female mice received 0, 312, 625, or 1,250 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed for 104 to 105 weeks. Average daily doses of 2,2-bis(bromomethyl)-1,3-propanediol were 35, 70, or 140 mg/kg (males) and 40, 80, or 170 mg/kg (females). Eight to 10 animals from each group were evaluated at 15 months.

Survival, Body Weights, Feed Consumption, and Clinical Findings

Survival of 1,250 ppm males and females was significantly lower than that of the controls. Mean body weights of exposed male and female mice were similar to controls throughout the study. Final mean body weights were also generally similar to those of controls. Feed consumption by exposed male and female mice was similar to that by controls. Clinical findings included tissue masses involving the eye in exposed mice.

Pathology Findings

Exposure of male mice to 2,2-bis(bromomethyl)-1,3-propanediol for 2 years was associated with neoplastic effects in the harderian gland, lung, and kidney. Exposure of female mice to 2,2-bis(bromomethyl)-1,3-propanediol was associated with increased incidences of neoplasms of the harderian gland, lung, and skin. Nonneoplastic effects in the lung were also observed in exposed females. These findings are outlined in the two summary tables.

GENETIC TOXICOLOGY

2,2-Bis(bromomethyl)-1,3-propanediol was mutagenic in *Salmonella typhimurium* strain TA100 when tested in the presence of induced 30% hamster liver S9; all other strain/activation combinations gave negative results. In cultured Chinese hamster ovary cells, 2,2-bis(bromomethyl)-1,3-propanediol induced chromosomal aberrations only in the presence of S9; no induction of sister chromatid exchanges was observed in cultured Chinese hamster ovary cells after treatment with 2,2-bis(bromomethyl)-1,3-propanediol, with or without S9. *In vivo*, 2,2-bis(bromomethyl)-1,3-propanediol induced significant increases in the frequencies of micronucleated erythrocytes in male and female mice. Significant increases in micronuclei were observed in peripheral blood samples from male and female mice exposed to 2,2-bis(bromomethyl)-1,3-propanediol for 13 weeks via dosed feed. Results of a bone marrow micronucleus test in male mice, where 2,2-bis(bromomethyl)-1,3-propanediol was administered by gavage, were considered to be equivocal due to inconsistent results obtained in two trials. An additional bone marrow micronucleus test was performed with male and female mice and 2,2-bis(bromomethyl)-1,3-propanediol was administered as a single intraperitoneal injection; results of this test were positive in females and negative in males.

CONCLUSIONS

Under the conditions of these 2-year feed studies, there was *clear evidence of carcinogenic activity** of 2,2-bis-(bromomethyl)-1,3-propanediol (FR-1138®) in male F344/N rats based on increased incidences of neoplasms of the skin, subcutaneous tissue, mammary gland, Zymbal's gland, oral cavity, esophagus, forestomach, small and large intestines, mesothelium, urinary bladder, lung, thyroid gland, and seminal vesicle, and the increased incidence of mononuclear cell leukemia.

There was *clear evidence of carcinogenic activity* of 2,2-bis(bromomethyl)-1,3-propanediol in female F344/N rats based on increased incidences of neoplasms of the oral cavity, esophagus, mammary gland, and thyroid gland.

There was *clear evidence of carcinogenic activity* of 2,2-bis(bromomethyl)-1,3-propanediol in male B6C3F$_1$ mice based on increased incidences of neoplasms of the harderian gland, lung, and kidney.

There was *clear evidence of carcinogenic activity* of 2,2-bis(bromomethyl)-1,3-propanediol in female B6C3F$_1$ mice based on increased incidences of neoplasms of the harderian gland, lung, and subcutaneous tissue.

Slight increases in the incidences of neoplasms of the pancreas and kidney in male rats; forestomach in male mice; and forestomach, mammary gland, and circulatory system in female mice may have also been related to treatment.

Exposure of male and female rats to 2,2-bis(bromomethyl)-1,3-propanediol was associated with alveolar/bronchiolar hyperplasia in the lung (males only); focal atrophy, papillary degeneration, transitional epithelial hyperplasia (pelvis), and papillary epithelial hyperplasia in the kidney; follicular cell hyperplasia in the thyroid gland (males only); hyperplasia in the seminal vesicle and pancreas (males only); mucosal hyperplasia in the forestomach (males only); and urinary bladder hyperplasia (males only). Exposure of mice to 2,2-bis(bromomethyl)-1,3-propanediol was associated with hyperplasia of the alveolar epithelium in females.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 13. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 15.

Summary of Site-Specific Carcinogenic Effects in Rats and Mice in the 2-Year Feed Studies of 2,2-Bis(bromomethyl)-1,3-propanediol

	Male Rats	Female Rats	Male Mice	Female Mice
Site				
Skin	+	−	−	−
Subcutaneous tissue	+	−	−	+
Mammary gland	+	+	−	±
Zymbal's gland	+	−	−	−
Oral cavity	+	+	−	−
Esophagus	+	+	−	−
Forestomach	+	−	±	±
Small intestine	+	−	−	−
Large intestine	+	−	−	−
Mesothelium	+	−	−	−
Kidney	±	−	+	−
Urinary bladder	+	−	−	−
Lung	+	−	+	+
Thyroid gland	+	+	−	−
Seminal vesicle	+	NA	−	NA
Hematopoietic system	+	−	−	−
Pancreas	±	−	−	−
Harderian gland	−	−	+	+
Circulatory system	−	−	−	±

+ = some or clear evidence
± = equivocal evidence
− = no evidence
NA = not applicable

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of 2,2-Bis(bromomethyl)-1,3-propanediol

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 2,500, 5,000, or 10,000 ppm and 20,000 ppm stop-exposure (equivalent to 0, 100, 200, or 430 mg/kg and 800 mg/kg)	0, 2,500, 5,000, or 10,000 ppm (equivalent to 0, 115, 230, or 460 mg/kg)	0, 312, 625, or 1,250 ppm (equivalent to 0, 35, 70, or 140 mg/kg)	0, 312, 625, or 1,250 ppm (equivalent to 0, 40, 80, or 170 mg/kg)
Body weights	10,000 ppm and 20,000 ppm stop-exposure groups lower than controls	10,000 ppm group lower than controls	Exposed groups similar to controls	Exposed groups similar to controls
2-Year survival rates	26/51, 20/53, 13/51, 1/55, 0/60	36/50, 27/51, 23/53, 5/52	42/50, 36/51, 35/50, 30/48	37/52, 30/50, 26/51, 11/50
Nonneoplastic effects	Kidney: focal atrophy (0/51, 0/53, 0/51, 5/55, 0/59); papillary degeneration (0/51, 5/53, 30/51, 29/55, 16/59); papillary epithelial hyperplasia (10/51, 20/53, 25/51, 47/55, 21/59); pelvis, transitional epithelium, hyperplasia (0/51, 0/53, 0/51, 4/55, 4/59) Lung: alveolar/ bronchiolar hyperplasia (3/51, 4/53, 5/51, 7/55, 14/60) Thyroid gland: follicular cell hyperplasia (1/51, 0/53, 2/51, 5/55, 6/59) Seminal vesicle: hyperplasia (1/51, 6/53, 4/51, 16/55, 33/60) Pancreas: focal hyperplasia (3/51, 9/53, 12/51, 14/53, 27/59) Forestomach: mucosal hyperplasia (4/51, 12/53, 6/51, 6/55, 6/59) Urinary bladder: hyperplasia (0/51, 0,53, 1/51, 3/55, 10/59)	Kidney: focal atrophy (0/50, 2/51, 1/53, 7/52); papillary degeneration (0/50, 1/51, 3/53, 17/52); papillary epithelial hyperplasia (0/50, 1/51, 1/53, 7/52)	None	Lung: alveolar epithelium, hyperplasia (1/52, 3/50, 8/51, 15/50)

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Neoplastic effects	Skin: squamous cell papilloma, keratoacanthoma, trichoepithelioma, basal cell adenoma, basal cell carcinoma, or squamous cell carcinoma (4/51, 6/53, 14/51, 24/55, 21/60) Skin, subcutaneous tissue: fibroma, fibrosarcoma, or sarcoma (2/51, 9/53, 13/51, 16/55, 10/60) Mammary gland: fibroadenoma or adenoma (0/51, 4/53, 7/51, 7/55, 5/60) Zymbal's gland: adenoma or carcinoma (2/51, 1/53, 4/51, 5/55, 15/60) Oral cavity (pharynx, tongue, or gingiva): squamous cell papilloma or carcinoma (0/51, 4/53, 9/51, 10/55, 13/60) Esophagus: squamous cell papilloma (0/51, 0/53, 1/51, 5/55, 0/60) Forestomach: squamous cell papilloma (0/51, 0/53, 0/51, 1/55, 5/60) Large intestine: adenoma or carcinoma (0/51, 0/53, 3/51, 4/55, 11/59) Small intestine: adenoma or carcinoma (0/51, 0/53, 0/51, 2/53, 5/59) Malignant mesothelioma: (0/51, 3/53, 8/51, 9/55, 26/60) Urinary bladder: transitional cell papilloma or carcinoma (0/51, 0/53, 1/51, 3/55, 2/59)	Oral cavity: squamous cell papilloma or carcinoma (2/50, 3/51, 5/53, 6/52) Esophagus: squamous cell papilloma (0/50, 0/51, 1/53, 10/52) Mammary gland: fibroadenoma (25/50, 45/51, 46/53, 45/52) Thyroid gland: follicular cell adenoma or carcinoma (0/50, 0/51, 2/53, 4/52)	Harderian gland: adenoma or carcinoma (4/50, 7/51, 16/50, 22/49) Lung: alveolar/ bronchiolar adenoma or carcinoma (15/50, 11/51, 16/50, 25/49) Kidney (renal tubule): adenoma (0/50, 0/51, 3/50, 2/49)	Harderian gland: adenoma or carcinoma (3/52, 12/50, 13/51, 19/50) Lung: alveolar/ bronchiolar adenoma or carcinoma (5/52, 5/50, 15/51, 19/50) Skin (subcutaneous tissue): sarcoma (0/52, 1/50, 4/51, 11/50)

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Neoplastic effects (continued)	Lung: alveolar/ bronchiolar adenoma or carcinoma (1/51, 1/53, 3/51, 4/55, 7/60); squamous cell carcinoma (0/51, 0/53, 0/51, 0/55, 3/60) Thyroid gland: follicular cell adenoma or carcinoma (0/51, 2/53, 6/51, 3/55, 9/59) Seminal vesicle: adenoma or carcinoma (0/51, 0/53, 0/51, 0/55, 2/60) Hematopoietic system: mononuclear cell leukemia (27/51, 29/53, 40/51, 34/55, 25/60)			
Uncertain effects	Kidney (renal tubule): adenoma (0/51, 0/53, 1/51, 3/55, 1/59) Pancreas: acinar cell adenoma (1/51, 2/53, 4/51, 3/53, 3/59)	None	Forestomach: squamous cell papilloma or carcinoma (0/50, 3/51, 3/50, 4/49)	Mammary gland: carcinoma (0/52, 0/50, 1/51, 3/50) Forestomach: squamous cell papilloma (0/52, 1/50, 5/51, 3/50) Circulatory system: hemangioma and hemangiosarcoma (1/52, 2/50, 0/51, 5/50)
Level of evidence of carcinogenic activity	Clear evidence	Clear evidence	Clear evidence	Clear evidence

Genetic toxicology

Salmonella typhimurium gene mutations:	Positive with S9 in strain TA100; negative in strains TA98, TA1535, and TA1537 with and without S9
Sister chromatid exchanges Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9
Chromosomal aberrations Cultured Chinese hamster ovary cells *in vitro*:	Positive with S9; negative without S9
Micronucleated erythrocytes Mouse bone marrow *in vivo* by gavage:	Equivocal in male mice
Mouse bone marrow *in vivo* by intraperitoneal injection:	Negative in male and positive in female mice
Mouse peripheral blood *in vivo*:	Positive in male and female mice

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on 2,2-bis(bromomethyl)-1,3-propanediol on November 29, 1994, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On November 29, 1994, the draft Technical Report on the toxicology and carcinogenesis studies of 2,2-bis(bromomethyl)-1,3-propanediol received public review by the National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. J.K. Dunnick, NIEHS, introduced the toxicology and carcinogenesis studies of 2,2-bis(bromomethyl)-1,3-propanediol by discussing the rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related neoplasms in rats and mice and possible compound-related nonneoplastic lesions in rats and female mice. The proposed conclusions for the studies were *clear evidence of carcinogenic activity* of 2,2-bis(bromomethyl)-1,3-propanediol in male and female F344/N rats and B6C3F$_1$ mice.

Dr. Russo, a principal reviewer, agreed with the proposed conclusions. She asked if there was more information on possible mutagenic or carcinogenic effects of the impurities detected in the compound or on the metabolism of 2,2-bis(bromomethyl)-1,3-propanediol and its contaminants. (The studies were conducted on commercially available fire retardant from the sole manufacturer, and no attempt was made to study impurities, contaminants, or metabolites.)

Dr. Ryan, the second principal reviewer, agreed with proposed conclusions. She questioned the rationale for dosed feed administration since the text suggested dermal and inhalation exposures were the most likely exposure routes for humans. Dr. Dunnick said the oral route was chosen to provide maximum exposure to the tissues. Dr. Ryan remarked on the large differences between the overall and adjusted incidence rates for several neoplasms and asked for discussion as to why. Dr. J.K. Haseman, NIEHS, said the adjusted rate provides an estimate of overall neoplasm incidence if all animals survive to the end of the study. In many cases this adjusted rate is reasonable, but it is less meaningful when there are only a few survivors as in the high dose groups of rats in the 2,2-bis(bromomethyl)-1,3-propanediol study.

Dr. Miller, the third principal reviewer, agreed with the proposed conclusions. She asked how the rodent doses would compare with likely human exposures and suggested that information be added as to the sources, routes, and degrees of human exposure. Dr. Dunnick responded that the one company that produces 2,2-bis(bromomethyl)-1,3-propanediol had not published information on worker exposure but noted that the Environmental Protection Agency has requested such information. Dr. J. Haartz, NIOSH, added that no information on 2,2-bis(bromomethyl)-1,3-propanediol was found in the National Occupational Exposure Survey, so there was no estimate of potentially exposed workers. Dr. Miller asked whether there should be concerns with vapor or pyrolysis products in the event of a fire. Dr. Dunnick said the chemical volatilizes at temperatures greater than 200° C and at high temperatures would form hydrogen bromide.

Dr. Miller moved that the technical report on 2,2-bis(bromomethyl)-1,3-propanediol be accepted with the revisions discussed and with the conclusions as written for male and female rats and mice, *clear evidence of carcinogenic activity*. Dr. Ryan seconded the motion, which was accepted unanimously with seven votes.